Submitting a CTA application to the MHRA

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1. **PURPOSE**

This SOP describes the procedure for applying for a Clinical Trial Authorisation (CTA) from the Medicines and Healthcare products Regulatory Agency (MHRA).

2. **INTRODUCTION**

The MHRA is the government agency responsible for ensuring that medicines and medical devices are safe.

A CTA is required only in trials of medicinal products. These are substances, or combinations of substances, which either prevent or treat disease in human beings or are administered to human beings with a view to making a medical diagnosis, or to restore, correct or modify physiological functions in humans.

Any research that fulfils the definition of a clinical trial, as described by the EU Directive 2001/20/EC Article 2 (a), will require a CTA from the Competent Authority in the Member State in which research is being carried out. A CTA will only be issued by the Competent Authority if it has no objections to the research proposal. The Competent Authority for the United Kingdom is the MHRA. The EU Directive has been transposed into UK law as the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments.

The EU Directive 2001/20/EC definition of a clinical trial is:

“…any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy”.

Clinical studies involving only medical devices, food supplements or other non-medicinal therapies (such as surgical interventions) are not covered by the EU Directive, but may require other regulatory approvals. Please see other SOPs for further details.

It is the responsibility of the Chief Investigator (CI) to establish whether regulatory approval is required for their study and that it is obtained prior to initiating the trial. The Joint Research Compliance Office (JRCO) can help with the determination of whether it is a clinical trial or not. The clinical trial algorithm can be found at [http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON009394&RevisionSelectionMethod=Latest](http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON009394&RevisionSelectionMethod=Latest)

3. **PROCEDURE**

3.1 **Procedure for obtaining a EudraCT number**
In order to provide a unique reference for clinical trials, each trial will need a EudraCT number. This number must be included on all clinical trial applications and as needed on other documents relating to the trial (e.g. safety reports). To obtain a EudraCT number, follow this process:

Apply for a security code via the EudraCT website

1. This will be sent to your email account and will expire after 24 hours.

2. Once you have your security code, request a EudraCT number via the EudraCT website by entering the security code along with:
   - Your organisation name
   - Organisation town/city
   - Organisation country
   - The sponsor’s protocol code number
   - Your name
   - The email address to which the EudraCT number will be sent
   - Member state(s) where the trial is anticipated to be conducted

3. The EudraCT number will be sent by email, which you should then save locally.
   The EudraCT number has the format: YYYY-NNNNNN-CC
   (Y = the year in which the number is issued)
   (N = a 6 digit sequential number)
   (C = check digit)

4. You need to print off the email containing the EudraCT number, to be sent as confirmation with the CTA application form to the MHRA and Ethics Committee applications.

5. The EudraCT Number must be included on all Clinical Trial applications within the Community and as needed on other documents relating to the trials (e.g. SUSAR reports).

3.2 Completing the CTA application form

There is a new application via the Integrated Research Application System (IRAS) found at: https://www.myresearchproject.org.uk/ which combines the ethics application along with an MHRA form. Investigators can either complete the MHRA form on the IRAS website or complete the CTA form via the EudraCT website.

The CTA application form can be accessed online via the EudraCT website. Detailed information on how to complete the form can be found on the MHRA website; you should ensure you check this website for the most up-to-date instructions on completing the form (http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=723).
Section A: Trial Identification
This section identifies your clinical trial by title and by EudraCT number. Where
the Trust or College is acting as the sponsor The Joint Research Compliance
Office (JRCO) reference number can be used as the Sponsor's Protocol Code
number. This number will be issued from the JRCO at the time of confirming
provisional sponsorship. The designated Competent Authority (CA) will be UK-
MHRA for UK only studies. If studies are conducted elsewhere in the EU, a CTA
should be submitted to each country’s CA.

Section B: Identification of the sponsor responsible for the request
This section identifies the name of the Sponsor organisation and relevant contact
details. Hence you must have a sponsorship letter from Imperial College
Academic Health Science Centre (AHSC) for your study before you can submit
your application. You will be required to provide a copy of the letter with the
completed form. For Imperial College AHSC Sponsored studies, the “name of
the person to contact” is Gary Roper, Head of Regulatory Compliance, Room
510C, 5th Floor, Lab Block, Charing Cross Hospital, Fulham Palace Road, W6
8RF, telephone: 020 3311 0204, fax: 020 3311 0203, email:
gary.roper@imperial.ac.uk.

If the sponsor of the study is not based in a member state of the EU, then a legal
representative who is based in the EU is necessary (as described in B2).

Section C: Applicant Identification
This section identifies you, the Applicant. This section is split into two parts: C1
- Application to the MS Competent Authority and C2 - Application to the Ethics
Committee. Both sections require completion. Sections should be completed
with the relevant details of the person making the application to the CA and
Research Ethics Committee. If you are applying on behalf of Imperial College
AHSC who are acting as Sponsor, then as such you are the person authorised by
the Sponsor to make the application.

Section D: Information on each IMP
This section asks for a description of, and information about, the Investigational
Medicinal Product(s) (IMP) being used in your study, including any comparator
drug(s). You will need to repeat this section if more than one test or comparator
product is being used. Much of the information required can be found on the
Summary of Product Characteristics (SmPC) (if the drug is already licensed) or
Investigator Brochure (IB). Each product will be given a number (e.g. PR1, PR2
etc) and should indicate whether this is a test product or a comparator.

Sections D1 to D3 should be completed for all products.

Sections D4 to D7 deals with specific types of products:
- D4 is for biological/biotechnological products
- D5 is for somatic cell therapy
- D6 is for gene therapy
- D7 is for placebos
There are two ways to add an active substance to your IMP: Active substance
details can either be filled in manually, or can be retrieved via an Active
Substances Search. To add an active substance manually, click the ‘add active
substance’ link and the ‘IMP Identification Details (Active Substances)’ screen will
appear.

Alternatively, if you are completing the form on the EudraCT website, you can use
the ‘search MPD to add active’ link to search the Medical Product Dictionary for
an active substance. The screen ‘D. MPD active Substance Search Criteria’
should appear. The active substance should be added for each IMP in the
study.

Section D8 asks about the release and supply of the investigational medicinal
product(s) from their manufacturing source. The section is split into two parts:
D.8.1 list IMPs and placebos for which no responsible site needs to be identified
and D.8.2 add responsible site

Section D.8.1 is used to identify IMPs and placebos that do not need to have
responsible sites identified, i.e. which:
- Have a Marketing Authorisation in the EU AND
- Are sourced from the EU market AND
- Are used in the trial without modification (e.g. not over encapsulated)
  AND
- The packaging and labelling is carried out for local use only as per

If all the above conditions are met, tick the appropriate box and indicate which
IMP these refer to.

Section 8.2 is dedicated to finished IMPs, i.e. medicinal products randomised,
packaged, labelled and certified for use in the clinical trial when conditions in 8.1
are not met. If there is more than one site, or more than one IMP is certified, then
give each IMP its number from section D.1.1 or D.7.2. In the case of multiple
sites indicate the product certified by each site.

For EU marketed products which are repackaged by a hospital pharmacy for use
in a clinical trial (i.e., off the shelf) enter ‘Hospital Packaging’ as Name of the
Organisation, along with the address of the Pharmacy Department for the
hospital.

**Section E: General Information on the trial**
This section is concerned with general information about the trial – disease
states, objectives, inclusion/exclusion criteria, end points, scope of the trial, study
design, duration, drug dosage etc. The majority of this information can be taken
from the study protocol.

The MedDRA (Medical Dictionary for Regulatory Activities) code can be found
using the search option. This only applies if completing the form on the EudraCT
website.

**Section F: Population of Trial Subjects**
This section is concerned with the subject population – age, gender, vulnerable groups, numbers, treatment afterwards, etc. Again, this information can be taken from the study protocol.

Section G: Proposed Trial Sites/Investigators in the Member State
This Section should be completed for the Chief Investigator, as well as all Principal Investigators in the case of multi-centre studies, and collaborators.

Question G4, relating to the sponsor’s delegation of duties to other organisations, should be answered in consultation with the JRCO as it will be project specific.

Section H: Competent Authority/Ethics Committee
This section asks for details regarding the ethics committee application. You will need to provide the name and address of the ethics committee as well as date of application (if already submitted) and the current status of the application, ie, the date and opinion of the ethics committee, if available. A copy of the CTA application should be included in the ethics application.

Section I: Signature
This is the signature page of the application and appears once you enable the PDF version of the form. The section outlines the responsibilities of the applicant. Make sure that you delete the appropriate wording so that the opening sentence reads “I hereby confirm on behalf of the sponsor that...”, and remember to only sign and date the section under ‘Applicant of the request for the Competent Authority’.

Section J: Check List
This is a checklist indicating all the relevant trial-related documentation supporting the application. Section 3.3 gives further information on the supporting documentation required. A copy of the checklist is found in Appendix 2.

3.3 Supporting documentation

In addition to the completed application form, you are also required to send supporting documentation. The additional information required will depend on the design of the trial. Appendix 1 outlines the additional data requirements for each type of trial. Appendix 2 demonstrates the supporting documents required for all Competent Authorities in the EU for all types of applications. Items that are shaded are not required to be sent to the MHRA. The minimum requirement for all studies is:

- Covering letter
- Clinical Trial Application + valid xml
- Protocol
- IB or document replacing the IB
- IMPD/simplified IMPD
- NIMP Dossier (if required)
- Scientific advice - A summary of scientific advice from any Member State or the EMA with regard to the clinical trial (if available).
• EMA Decision - A copy the EMA’s Decision on the decision of the Paediatric Investigation Plan and the opinion of the Paediatric Committee (if applicable).
• The content of the labeling of the IMP (or justification for its absence)
• Proof of payment
• Manufacturer’s authorisation or Importer’s authorisation plus QP declaration on GMP for each manufacturing site.

The outline of all active trials should be submitted by the Chief Investigator for all studies with the same IMP in their department, and not by Sponsor as indicated in the MHRA guidance. This has been agreed by the MHRA for non-commercial trials.

It is very important that all the required documentation for your particular application is submitted to the MHRA with your CTA application. If the application is received in the wrong format or with documentation missing, it may be returned as an ‘invalid submission’.

It is best practice to include a cover letter with your CTA application. An example can be found in Appendix 5.

3.4 How and where to apply?

Applicants should submit documents electronically on disk, with one PDF file for each document. The MHRA will not accept paper documents.

In exceptional cases where the use of PDF files is not feasible, (for example, in the case of small, non-commercial clinical trials) electronic documents using Word are acceptable and will be processed to the same target timescales. Disks should be submitted with no subdirectory structure.

The following disk formats are acceptable:

• CD-ROM
• CD-R
• CD-RW
• DVD-R
• DVD-RW

The following formats are not acceptable:

• DVD-ROM
• DVD-RAM

Applications are required to be submitted as electronic documents on disk, with one PDF file for each document. In extreme cases PDF files is not feasible, (for example, in the case of small, non-commercial clinical trials) electronic documents using Word are acceptable and will be processed to the same target timescales. Disks should be submitted with no subdirectory structure.
Each disk should be labeled in the following manner:

- EudraCT number
- Description of contents e.g.
  - Initial Application
  - Response to Remarks from an Initial Application
- Company name
- Date sent

The disk may be printed or labeled with an adhesive paper label or a permanent marker pen.

Further information on the standards and conventions for submitting electronic documents, including the acceptable file name, can be found here: [http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&ssDocName=CON2024282&ssSourceNodeId=723&ssTargetNodeId=380](http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&ssDocName=CON2024282&ssSourceNodeId=723&ssTargetNodeId=380).

Once the form has been completed, save the core data set as an XML file using the utilities feature linked to the form on the EudraCT webpage or IRAS website. You need to send a copy of the XML file on disk along with the supporting documentation and full application as PDF files. A signed copy of the CTA should also be included on disk.

The signature page of the application form must be signed for inclusion on the disk. Either insert a signature image into the Word document (e.g. copy image “Paste Special>Picture (Windows metafile)”) prior to conversion to PDF, or print, sign, scan and then merge the signature page with the relevant PDF. Signatures are not required in the case of cover letters. The MHRA do not currently accept digital signatures.

All disks and the full application (including xml file) should be sent to the address below:

Information Processing Unit  
Area 6  
MHRA  
Market Towers, 1 Nine Elms Lane  
London SW8 5NQ

### 3.5 How do I pay the fees?

MHRA CTA/Dossier fees at time of submission are a legal requirement specified in the MHRA Fees Regulations. Acceptable methods of payment are listed below, payment at a different time e.g. on an invoice is not acceptable.
Proof of payment must be clearly mentioned in the covering letter and/or as a separate document (e.g. photocopy of cheque / confirmation of bank transfer).

The MHRA charge a fee for each CTA application submitted. A guideline on fees is provided in Appendix 1, but you should check the MHRA website for the current scale for charges. How you intend to pay should be indicated on the covering letter.

3.5.1 Payment by cheque
Cheques should be made payable to the Medicines and Healthcare products Regulatory Agency, with the EudraCT number, product name, protocol code and CTA number (where available) stated on the back. Cheques should be sent to:

Finance Department MHRA
Market Towers
1 Nine Elms Lane
London SW8 5NQ

3.5.2 Payment by bank transfer
Remittances should be sent to the attention of Cashier, or fax to 020 3 080 6524 or e-mail to cashiers@mhra.gsi.gov.uk
MHRA Cashiers
5th Floor
151 Buckingham Palace Road
London
SW1W 9SZ

MHRA Bank Account Details for Bank Transfer:

Account Number: 12314800
Sort Code: 08-33-00
Swift code: CITIGB2L
Iban: GB05CITI08330012314800
Branch Address:
Citibank N.A.
London Branch
Canary Wharf
London
E14 5LB

BACS Payments
Bank Name: Bank of England.
Sort Code: 10-14-99.
Account Number: 06781000.
Bank Address: Government Counter, Threadneedle Street, London, EC2R 8AH.
Sterling CHAPS Payment from a UK Account
Bank Name: Natwest Bank
Sort Code: 16-53-60
Account Number: 6781
Reference: MHRA
Bank Address: 6 Coldharbour Lane, Hayes, Middlesex, UB3 3EL

Sterling to Sterling receipt from an overseas bank account (Cross-Border)
Information that the remitter must quote on the payment instruction
Amount: In Sterling
Account with Institution (field 57A): NWBKGB2LXXX
Beneficiary Customer (field 59): IBAN GB82NWBK60104341414985
Remittance Information (Field 70 – up to 4 lines of 32 characters):
Customer’s OPG Sterling account number (i.e. 4 or 5 digits), plus any reference information

Foreign Currency (non Euro) to Sterling receipt from an overseas bank account (Cross-Border)
Information that the remitter must quote on the payment instruction
Amount: In Foreign Currency
Account with Institution (field 57A): NWBKGB2LXXX
Beneficiary Customer (field 59): IBAN GB82NWBK60104341414985
Remittance Information (Field 70 – up to 4 lines of 32 characters):
Customer’s OPG Sterling account number (i.e. 4 or 5 digits), plus any reference information

Euro to Sterling receipt from a UK bank account (Domestic) or Overseas bank account (Cross-Border)
Information that the remitter must quote on the payment instruction
Account with Institution (field 57A): NWBKGB2LXXX
IBAN: (field 59- the IBAN should be quoted in the account field):
GB43NWBK60720608304793
Account Name:(field 59): Office of HM Paymaster General Euro Receipt Account
Amount: In Euro
Reference Information (Field 70 – up to 4 lines of 32 characters):
Customer’s OPG Sterling account number (i.e. 4 or 5 digits), plus any reference information

Payments can be made in British Pounds Sterling only.
Enquiries to:
MHRA head office: 020 3080 6000.

MHRA
5th Floor
151 Buckingham Palace Road
London
SW1W 9SZ
The EudraCT number should be included with payment. Proof of payment should be included in the application sent to the Clinical Trials Unit at the MHRA.

3.6 Do I have to apply anywhere else?

All clinical trials also require a favourable opinion from an Ethics Committee.

3.7 What happens next?

The CTA will be validated on receipt and an acknowledgement letter will be sent to the person submitting the application (as notified in section C1). If the application is valid then the assessment period will begin. This starts from the date of receipt of a valid application. If the application is not valid then the person making the application will be told of the deficiencies. Nothing will happen to the application until the missing components are provided.

3.8 What is the timeframe?

The initial assessment will be performed within 30 days. For phase I healthy volunteer trials, the assessment period will be 21 days maximum, with an average of 14 days. For the purposes of this calculation, the day of receipt of the valid application by the MHRA Clinical Trials Unit is day 0.

The MHRA must provide an initial response to all valid applications within 30 days of receipt (21 days for phase I healthy volunteer studies). If you have not received a letter within 35 days of sending the application, please email RIS.CT@mhra.gsi.gov.uk. The MHRA will not accept calls or emails prior to 35 days to check the progress of the submission.

3.9 What are the possible outcomes?

There are two possible outcomes:

- Acceptance (with or without conditions)
- Grounds for non-acceptance.

Some acceptance letters state conditions or remarks. The remarks must be responded to prior to the start of the study.

If there are grounds for non-acceptance, the investigator should reply within 14 days (30 days for gene therapy, somatic cell therapy or products containing genetically modified organisms) to submit an amended request for authorisation. These periods may be extended in certain circumstances.

The amended request is assessed within a total of 60 days from receipt of the initial application (90 days for gene therapy products) and there are two possible outcomes:
• Acceptance (with or without conditions)
• Grounds for non-acceptance.

Once you have received approval from the MHRA you may start the trial, subject to receiving favourable opinion from the ethics committee and approval from the NHS Trust(s) Research and Development Office.

Please note that as of 1 November 2007, letters from the MHRA relating to clinical trial submissions will not be signed.

3.10 Terms and conditions of approval

3.10.1 For a multi centre trial, the MHRA must be notified of each additional investigator using the Annex 2: Notification of an Amendment form. Ethics approval for each additional investigator should also be obtained via a Site Specific Assessment (SSA).

3.10.2 In accordance with regulation 27, you must notify the Competent Authority within 90 days of the conclusion of the trial.

3.10.3 The MHRA may suspend or terminate a clinical trial where it feels the conditions for authorisation are not being met.

3.11 Can I make changes after receiving an authorisation?

3.11.1 Non-substantial amendments
The CI can make non-substantial amendments at any time but must keep records of these amendments.

3.11.2 Substantial amendments
For substantial amendments, the Annex 2: Notification of an Amendment form must be used. Other documents required are:
• Description of the amendment
• Reasons for the proposed amendment
• Copy of the proposed changes to the protocol or any other documents
• Supporting data for the amendment, including any change to the risk benefit analysis

Further details on what constitutes substantial amendments can be found in the SOP on protocol amendments available from the JRCO. All amendments submitted to the MHRA should be done electronically, preferably on disk (as the original submission). Information on amendments to the MHRA can be found at http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/ Clinicaltrials/Maintainingaclinicaltrialauthorisation(CTA)-Amendmentsandtrialconclusion/index.htm
3.12 Who reports adverse drug reactions and adverse drug events?

All SAEs related to the medicinal product and unexpected events not listed in the protocol as an expected occurrence should be notified to the ethics committee, the MHRA and all Safety Reports should be forwarded to the sponsor annually (see 3.14). The CI shall keep detailed records of all adverse events relating to a clinical trial which are reported to him by the investigators for that trial.

3.13 Who reports suspected unexpected serious adverse reactions?

The Chief Investigator shall ensure that all relevant information about a suspected unexpected serious adverse reaction (SUSAR) which occurs during the course of a clinical trial in the United Kingdom is reported as soon as possible to the MHRA, the relevant ethics committee and the Sponsor. For fatal or life-threatening SUSARs, this needs to be done within 7 days of the CI becoming aware of the reaction. All other SUSARs should be reported within 15 days of the CI becoming aware of the event.

These reports or information may be provided on paper using the CIOMS form or by entering the report or information in the European (Eudravigilance) Adverse reaction reporting. Further guidance can be found in the Safety Reporting SOP.

3.14 When is the annual safety report due?

The annual Development Safety Update Report (DSUR) is due on the anniversary of the CTA approval and a copy should be sent to the Sponsor. Further guidance can be found in the Safety Reporting SOP.

3.15 What happens when the trial ends?

A notification of the end of the trial should be sent by the CI and copied to the Sponsor within 90 days of its conclusion.

4. REFERENCES

1) EU Clinical Trials Directive 2001/20/EC
2) Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of a substantial amendment and declaration of the end of the trial, April 2004
3) Description of the Medicines for Human Use (Clinical Trials) Regulations 2004
4) SOP on Amendments to Healthcare Research, ref: JRCO/SOP/006
5) SOP on Safety Reporting, ref: JRCO/SOP/001
6) SOP on IMP Management and Accountability, ref: JRCO/SOP/026
5. APPENDICES

5.1 Appendix 1: Summary of data required for CTA application and substantial amendments to a clinical trial

For authorisation of a clinical trial – please follow link below for most up-to-date information
http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Applyingforaclinicaltrialauthorisation/Howmuchdoesitcost/#l2

For substantial amendments to a clinical trial – please follow link below for most up-to-date information
http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/ManagingyourCTA/Amendments/Fees/index.htm
### 5.2 Appendix 2: Checklist of the information appended to the application form

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<th>EC</th>
<th>INFORMATION PROVIDED</th>
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<tr>
<td>1</td>
<td>General</td>
<td>1.1 Receipt of confirmation of EudraCT number</td>
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<tr>
<td></td>
<td></td>
<td>1.2 Covering letter</td>
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<tr>
<td></td>
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<td>1.3 Application form</td>
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<td></td>
<td></td>
<td>1.4 List of Competent Authorities within the Community to which the application has been submitted and details of decisions</td>
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<td></td>
<td>1.5 Copy of ethics committee opinion in the MS concerned when available</td>
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<td>1.6 Copy/summary of any scientific advice</td>
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<td>1.7 If the applicant is not the sponsor, a letter of authorisation enabling the applicant to act on behalf of the sponsor</td>
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<tr>
<td>2</td>
<td>Subject related</td>
<td>2.1 Informed consent form</td>
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<td>2.2 Subject information leaflet</td>
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<td></td>
<td>2.3 Arrangements for recruitment of subjects</td>
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<tr>
<td>3</td>
<td>Protocol related</td>
<td>3.1 Clinical trial protocol with all current amendments</td>
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<td></td>
<td></td>
<td>3.2 Summary of the protocol in the national language</td>
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<td>3.3 Peer review of trial when available</td>
</tr>
<tr>
<td></td>
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<td>3.4 Ethical assessment made by the principal/coordinating investigator, if not given in the application form or protocol</td>
</tr>
<tr>
<td>4</td>
<td>IMP related</td>
<td>4.1 Investigator’s brochure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.2 Investigational Medicinal Product Dossier (IMPD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.3 Simplified IMPD for known products</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.4 Summary of Product Characteristics (SmPC) (for products with marketing authorisation in the Community)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.5 Outline of all active trials with the same IMP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.6 If IMP manufactured in E.U. and if no marketing authorisation in EU:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.6.1 Copy of the manufacturing authorization referred to in Art. 13.1. of the Directive stating the scope of this authorization</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.7 If IMP not manufactured in E.U. and if no marketing authorisation in EU:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.7.1 Certification of the QP that the manufacturing site works in compliance with GMP at least equivalent to EU GMP, or that each production batch has undergone all relevant analyses, tests or checks necessary to confirm its quality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.7.2 Certification of GMP status of active biological substance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.7.3 Copy of the importers manufacturing authorization referred to in Art. 13.1. of the Directive stating the scope of this authorization</td>
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<tr>
<td></td>
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<td>4.8 Certificate of analysis for test product in exceptional cases:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.8.1 Where impurities are not justified by the specification or when unexpected impurities (not covered by specification) are detected</td>
</tr>
<tr>
<td>CA</td>
<td>EC</td>
<td>INFORMATION PROVIDED</td>
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<td>4.9 Viral safety studies when applicable.</td>
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<td>4.10 Applicable authorisations to cover trials or products with special characteristics (if available) e.g. GMOs, radiopharmaceuticals</td>
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<tr>
<td></td>
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<td>4.11 TSE Certificate when applicable</td>
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<tr>
<td></td>
<td></td>
<td>4.12 Examples of the label in the national language</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>Facilities &amp; staff related</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.1 Facilities for the trial</td>
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<tr>
<td></td>
<td></td>
<td>5.2 CV of the coordinating investigator in the MS concerned (for multicentre trials)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.3 CV of each investigator responsible for the conduct of a trial in a site in the MS concerned (principal investigator)</td>
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<tr>
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<td></td>
<td>5.4 Information about supporting staff</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>Finance related</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.1 Provision for indemnity or compensation in the event of injury or death attributable to the clinical trial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.2 Any insurance or indemnity to cover the liability of the sponsor or investigator</td>
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<tr>
<td></td>
<td></td>
<td>6.3 Compensation to investigators</td>
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<tr>
<td></td>
<td></td>
<td>6.4 Compensation to subjects</td>
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<tr>
<td></td>
<td></td>
<td>6.5 Agreement between the sponsor and the trial site</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.6 Agreement between the investigators and the trial sites</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.7 Certificate of agreement between sponsor and investigator when not in the protocol</td>
</tr>
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### Appendix 3: Outline of Protocol for Proposed Trial

<table>
<thead>
<tr>
<th>1. ADMINISTRATIVE INFORMATION</th>
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<tbody>
<tr>
<td>Name of sponsor</td>
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<tr>
<td>Name of the investigational medicinal product</td>
</tr>
<tr>
<td>Eudract number for proposed trial</td>
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<table>
<thead>
<tr>
<th>2. CLINICAL USE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical condition or disease under investigation</td>
</tr>
<tr>
<td>Any other medical condition or disease under investigation with this product</td>
</tr>
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<table>
<thead>
<tr>
<th>3. DATE OF PROTOCOL OVERVIEW SUBMISSION</th>
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<table>
<thead>
<tr>
<th>4. TITLE OF CLINICAL TRIAL</th>
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<table>
<thead>
<tr>
<th>5. PURPOSE OF CLINICAL TRIAL</th>
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<table>
<thead>
<tr>
<th>6. DESIGN OF CLINICAL TRIAL</th>
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<table>
<thead>
<tr>
<th>7. PATIENT POPULATION IN CLINICAL TRIAL</th>
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<table>
<thead>
<tr>
<th>8. MAXIMUM NUMBER OF PATIENTS TO BE INCLUDED IN CLINICAL TRIAL</th>
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<thead>
<tr>
<th>9. MAIN INCLUSION CRITERIA IN CLINICAL TRIAL</th>
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<tr>
<th>10. MAIN EXCLUSION CRITERIA IN CLINICAL TRIAL</th>
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<table>
<thead>
<tr>
<th>11. PROCEDURES FOR SAFETY MONITORING DURING TRIAL</th>
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<table>
<thead>
<tr>
<th>12. CRITERIA FOR WITHDRAWAL OF PATIENTS ON SAFETY GROUNDS</th>
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<table>
<thead>
<tr>
<th>13. ROUTE(S) OF ADMINISTRATION (use standard terms)</th>
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<table>
<thead>
<tr>
<th>14. MAXIMUM DOSAGE ALLOWED (specify daily or total)</th>
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<tr>
<th>15. MAXIMUM DURATION OF TREATMENT OF A SUBJET</th>
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<table>
<thead>
<tr>
<th>16. ACTIVE COMPARATOR PRODUCT(S)</th>
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<table>
<thead>
<tr>
<th>17. ON-GOING TRIALS IN OTHER EU MEMBER STATES</th>
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<table>
<thead>
<tr>
<th>18. REGULATORY SUBMISSIONS ON SAFETY GROUNDS</th>
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### 5.4 Appendix 4: Outline of all active trials with an Investigational Medicinal Product

<table>
<thead>
<tr>
<th>For official use:</th>
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<tbody>
<tr>
<td>Date received ________________________  Date approved __________________________</td>
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<tr>
<td>CTA no. _____________________________</td>
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</table>

<table>
<thead>
<tr>
<th>1. ADMINISTRATIVE INFORMATION</th>
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<tr>
<td>Eudract number for proposed trial</td>
</tr>
<tr>
<td>Eudract number for first trial undertaken</td>
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<tr>
<td>Eudract number(s) for subsequent trial(s)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>2. CLINICAL USE</th>
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<tbody>
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<th>11. CRITERIA FOR WITHDRAWAL OF PATIENTS ON SAFETY GROUNDS IN ON-GOING TRIAL(S)</th>
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<table>
<thead>
<tr>
<th>12. ROUTE(S) OF ADMINISTRATION (USE STANDARD TERMS)</th>
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<table>
<thead>
<tr>
<th>13. MAXIMUM DOSAGE ALLOWED IN ON-GOING TRIAL(S) (specify daily or total)</th>
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</thead>
</table>

**Note: This should be completed by department.**
5.5 Appendix 5: Sample Cover Letter

<Date>

MHRA

Medicines and Healthcare products Regulatory Agency
151 Buckingham Palace Road
Victoria
London
SW1W 9SZ

To whom this may concern,

Re: <name of study>

EudraCT Number:

Please find enclosed an application for clinical trial authorisation for the above study. The IMPs in this trial are xxx. I have been informed by staff at the MHRA that this study qualifies as a xxxx type study and the required payment of £xxx will be paid via xxx.

No other application has been made to any other Competent Authorities.

Please do not hesitate to contact me should you require any further information.

Yours faithfully,

< Chief Investigator>

cc Joint Research Compliance Office, 5th Floor, Lab Block, Charing Cross Hospital, Fulham Palace Road, W6 8RF